REMARKS

I. Rejection of Claims 18, 23, and 24 Under 35 U.S.C. § 102(b) or § 102(e).

The Examiner rejected claims 18, 23, and 24 under 35 U.S.C. § 102(b) or § 102(e) as allegedly "being anticipated by any one of Rashtchian et al., Stemmer et al., Stemmer (US 5,514,568), or Jones (US 5,286,632)." Office Action at page 2, item 1. According to the Examiner, each of the cited documents disclose the methods recited in claims 18, 23, and 24. *Id.* at pages 2-3. Because none of the cited documents teach each and every element of the claims, Applicants respectfully traverse the rejection.

First, Applicants point out that the Examiner did not fully identify the citation for either "Rashtchian et al." or "Stemmer et al." In responding to the Examiner's contentions, Applicants have presumed that by "Rashtchian et al.," the Examiner meant Rashtchian, et al., PCR Methods and Applications 2:124-130 (1992). Rashtchian et al. was cited on PTO Form 892 that accompanied the Office Action mailed on August 15, 2005, in this application. In addition, Applicants have presumed that by "Stemmer et al.," the Examiner meant Stemmer and Morris, BioTechniques 13:214-220 (1992). Stemmer and Morris was listed on Form PTO/SB/08 that was filed with an Information Disclosure Statement on August 5, 2004, in this application. To maintain consistency with the language of the Office Action, and to avoid confusion with another document listed on the same Form PTO/SB/08 filed on August 5, 2004 (Stemmer et al., BioTechniques 14:256-265 [1993]), Applicants refer to Stemmer and Morris as "Stemmer et al. 1992" in this paper.

In rejecting the claims, the Examiner stated that "[c]laim 18 is drawn to a method comprising the use of a first and second mutagenic primer which overlap in sequence,

with a double-stranded circular DNA molecule, and synthesis of mutagenized DNA by linear cyclic amplification." Office Action at page 2. The Examiner also stated that "[c]laim 23 comprises the additional steps of annealing the mutagenized strands and transforming a host cell, [and] claim 24 comprises the additional step of digesting the DNA molecule for mutagenesis." *Id.* According to the Examiner, Rashtchian et al., Stemmer et al. 1992, Stemmer, and Jones disclose such methods. *Id.* at pages 2-3.

Claims 18 and 24 recite a method comprising "a linear cyclic amplification reaction." Claim 23 depends from claim 18, and thus, also comprises "a linear cyclic amplification reaction." Although the methods described in the specification are not limited to "linear cyclic amplification," claims 18 and 24 expressly recite that element.

In alleging that Rashtchian et al. teaches the methods of claims 18, 23, and 24, the Examiner referred to "pages 124-129, especially Fig. 1 on page 126." *Id.* at page 2. Nowhere in those pages does Rashtchian et al. teach or suggest "a linear cyclic amplification reaction," according to the methods of claims 18, 23, and 24. Instead, Rashtchian et al. discusses site-directed mutagenesis methods that only use PCR amplification reactions. *See, e.g.*, Rashtchian et al., p. 124 ("In this paper, we report a modification of the UDG cloning method for generation of site-specific mutations by PCR"); p. 125, the entire paragraph entitled "PCR amplification," which discusses the PCR amplification reaction conditions used throughout the paper; p. 125, the paragraph entitled "mutagenesis," ("All PCR reactions for mutagenesis . . ."); and Fig. 1, p. 126: Fig. 1 (A) shows mutagenesis comprising a single PCR amplification reaction, while Fig.1 (B) shows mutagenesis comprising two PCR amplification reactions. Nowhere

does Rashtchian et al. discuss the linear cyclic amplification reactions according to claims 18, 23, and 24.

PCR amplification reactions are different from linear cyclic amplification reactions as explained in the present specification. For example, the present specification explains that "[l]inear cyclic amplification reactions . . . differ significantly from the polymerase chain reaction (PCR)." See present specification at page 6, line 36 to page 7, line 3. In particular, the specification explains that:

> The polymerase chain reaction produces an amplification product that grows exponentially in amount with respect to the number of cycles. Linear cyclic amplification reactions differ from PCR because the amount of amplification product produced in a linear cyclic amplification reaction is linear with respect to the number of cycles performed.
>
> *Id.* at page 7, lines 3-9.

Thus, Rashtchian et al. fails to teach or suggest each and every element of claims 18, 23, and 24 because it does not teach or suggest at least a linear cyclic amplification reaction. Accordingly, for at least that reason, claims 18, 23, and 24 are not anticipated by Rashtchian et al. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 18, 23, and 24 under 35 U.S.C. § 102(b) as allegedly being anticipated by Rashtchian et al.

In alleging that Stemmer et al. 1992 teaches the methods of claims 18, 23, and 24, the Examiner referred to "Fig. 3 on page 219." Office Action at page 2. Stemmer et al. 1992, like Rashtchian et al., also fails to teach or suggest "a linear cyclic amplification reaction," according to the methods of claims 18, 23, and 24. Like Rashtchian et al., Stemmer et al. 1992 discusses mutagenesis methods that only use PCR amplification reactions. Fig. 3 on page 219 of Stemmer et al. 1992, expressly

describes "the general scheme for EIPCR. EIPCR involves 6 steps: PCR, fill-in, digestion, purification (optional), ligation and transformation." Nowhere does Stemmer et al. 1992 discuss the linear cyclic amplification reactions according to claims 18, 23, and 24.

As discussed above, PCR amplification reactions are different from linear cyclic amplification reactions. Thus, Stemmer et al. 1992 fails to teach or suggest each and every element of claims 18, 23, and 24 because it does not teach or suggest at least a linear cyclic amplification reaction. Accordingly, for at least that reason, claims 18, 23, and 24 are not anticipated by Stemmer et al. 1992. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 18, 23, and 24 under 35 U.S.C. § 102(b) as allegedly being anticipated by Stemmer et al. 1992.

In alleging that Stemmer (U.S. Patent No. 5,514,568) ("Stemmer '568 patent") teaches the methods of claims 18, 23, and 24, the Examiner referred to "columns 5-9 and Fig.1." Office Action at page 3. Stemmer '568 patent, like Stemmer et al. 1992 and Rashtchian et al., also fails to teach or suggest "a linear cyclic amplification reaction," according to the methods of claims 18, 23, and 24. Stemmer '568 patent discusses mutagenesis methods that only use PCR amplification reactions. For example, Fig. 1 of Stemmer '568 patent "is a schematic diagram outlining the steps of EIPCR." Stemmer '568 patent, Fig. 1 and col. 3, lines 14-15. Stemmer '568 patent further explains that "Enzymatic Inverse Polymerase Chain Reaction (EIPCR) is a PCR-based method for performing site-directed mutagenesis." *Id.* at col. 5, lines 41-43. Nowhere does Stemmer '568 patent discuss the linear cyclic amplification reactions according to claims 18, 23, and 24.

As discussed above, PCR amplification reactions are different from linear cyclic amplification reactions. Thus, Stemmer '568 patent fails to teach or suggest each and every element of claims 18, 23, and 24 because it does not teach or suggest at least a linear cyclic amplification reaction. Accordingly, for at least that reason, claims 18, 23, and 24 are not anticipated by Stemmer '568 patent. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 18, 23, and 24 under 35 U.S.C. § 102(b) or (e) as allegedly being anticipated by Stemmer '568 patent.

In alleging that Jones (U.S. Patent No. 5,286,632) teaches the methods of claims 18, 23, and 24, the Examiner referred to "Fig. 1 and columns 3, 5, 9, and 10." Office Action at page 3. Jones, like Stemmer '568 patent, Stemmer et al. 1992 and Rashtchian et al., also fails to teach or suggest "a linear cyclic amplification reaction," according to the methods of claims 18, 23, and 24. Jones discusses mutagenesis methods that only use PCR amplification reactions. *See, e.g.,* col. 2, summary of the invention, lines 39-42 ("the present invention relates to a method for synthesizing a double-stranded DNA molecule, using the polymerase chain reaction (PCR) process. . . ."). Cols. 3, 5, 9 and 10, and Fig. 1 similarly discuss mutagenesis by means of PCR only. Nowhere does Jones discuss the linear cyclic amplification reactions according to claims 18, 23, and 24.

As discussed above, PCR amplification reactions are different from linear cyclic amplification reactions. Thus, Jones fails to teach or suggest each and every element of claims 18, 23, and 24 because it does not teach or suggest at least a linear cyclic amplification reaction. Accordingly, for at least that reason, claims 18, 23, and 24 are not anticipated by Jones. Therefore, Applicants respectfully request reconsideration

and withdrawal of the rejection of claims 18, 23, and 24 under 35 U.S.C. § 102(b) or (e) as allegedly being anticipated by Jones.

Because the Examiner fails to establish that any of the cited documents anticipate any of claims 18, 23, or 24 under § 102(b) or (e) for at least the reasons discussed above, Applicants do not need to address the Examiner's contentions concerning other elements of those claims. By not addressing those contentions, Applicants in no way acquiesce to those contentions.

II. Rejection of Claims 19-22 Under 35 U.S.C. § 103(a).

The Examiner rejected claims 19-22 under 35 U.S.C. § 103(a) as allegedly "being unpatentable over any one of Rashtchian et al., Stemmer et al., Stemmer (US 5,514,568), or Jones (US 5,268,632)."[1] Office Action at page 3, item 2. Applicants respectfully traverse the rejection.

The Examiner alleged that "[t]hese claims are drawn to the method of claim 18 . . . with further limitations relating to Pfu polymerase, 5'-phosphorylated primers, less than 20 amplification cycles, and completely complementary first and second primers." *Id.* at pages 3-4. According to the Examiner, "[o]ne of ordinary skill in the art would have been motivated to apply these further limitations in the method of any one of the cited primary references. . . ." *Id.* at page 4. The Examiner further contended that "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods." *Id.*

[1] As discussed in section I above, Applicants presume that by "Rashtchian et al.," the Examiner meant Rashtchian, et al., PCR Methods and Applications 2:124-130 (1992); and that by "Stemmer et al.," the Examiner meant Stemmer and Morris, BioTechniques 13:214-220 (1992) ("Stemmer et al. 1992").

Applicants assert that the Examiner has failed to establish a *prima facie* case of obviousness. As set forth in the M.P.E.P. at § 2143 at page 2100-129, three basic criteria must be met:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

As discussed above, none of the cited documents teach or suggest "a linear cyclic amplification reaction" according to independent claim 18. Each of claims 19-22 depend from claim 18, and thus, also comprise "a linear cyclic amplification reaction." Accordingly, for at least that reason, none of the cited documents, either alone or in combination, teach or suggest all of the elements of claims 18-22. Applicants, therefore, respectfully assert that the Examiner has not established a *prima facie* case of obviousness. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 19-22 under 35 U.S.C. § 103(a) as allegedly being obvious in view of any one of Rashtchian et al., Stemmer et al. 1992, Stemmer '568 patent, or Jones.

Because the Examiner fails to establish that claims 19-22 would have been obvious for at least the reasons discussed above, Applicants need not address the Examiner's contentions concerning other elements of those claims. By not addressing those contentions, applicants in no way acquiesce to those contentions.

III. Obviousness-type Double Patenting Rejections

The Examiner rejected claims 18-24 under the judicially created doctrine of obviousness-type double patenting in view of certain claims of U.S. Patent Nos. 5,789,166, 5,932,419, 6,391,548, and 6,713,285. Office Action at pages 4-5. If the Examiner determines that claims 18 to 24 are otherwise allowable, Applicants will file a terminal disclaimer.

CONCLUSION

If the Examiner does not consider the application to be allowable, the undersigned requests that, prior to taking action, the Examiner call her at (650) 849-6749 to set up an interview.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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